IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Art Unit	: 1646	**Customer No.: 035811**
Examiner	: Nirmal Singh Basi	
Serial No.	: 09/129,758	
Filed	: August 5, 1998	
Inventors	: Rainer Waldmann	Docket No.: 1099-00
	: Frederic Bassilana	
	: Eric Lingueglia	Confirmation No.: 5113
	: Michel Lazdunski	
	: Catherine Heurteaux	
	: Guy Champigny	
Title	: MAMMAL NEURONAL ACID	
	: SENSING CATIONIC CHANNEL,	
	: CLONING AND APPLICATIONS THEREOF	

DECLARATION OF PETER MCNAUGHTON UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I hereby declare as follows:

1. I, Peter Anthony McNaughton, am a University Professor in Pharmacology. A copy of my curriculum vitae is attached hereto as Exhibit A.

2. I have read and understood U.S. Patent Application No. 09/129,758 (the "Application"), and have read the Official Action dated November 29, 2006 concerning the Application.

3. The November 29, 2006 Official Action states that the claimed subject matter is not supported by either a credible, specific, and substantial asserted utility or a well established utility. Thus, I understand that the Examiner believes that the Application does not disclose a specific function that the claimed cationic channel possesses, nor any disease states that are directly related to the claimed channel. The November 29, 2006 Official Action also states that,

because there supposedly is no utility, the Application does not adequately enable one of ordinary skill in the art to make and use the claimed subject matter.

4. I consider one of ordinary skill in this art to be a person knowledgeable in the field of ion channels and their functions; and also expert in the technologies mentioned in the patent application, namely the cloning and electrophysiological characterization of novel ion channels, and the investigation of their physiological roles in humans and animals through the use of suitable techniques such as investigation of animals in which the channels have been deleted, and exploration of the physiological responses of humans following administration of compounds aimed at interfering with the operation of the channels. I have published papers in all these fields (see attached CV) and I therefore consider myself to be appropriately skilled to judge this application

5. Concerning the utility of acid-sensing ionic channels (ASICs), I consider that the information contained in the Application is sufficient to allow one of ordinary skill in the art to conclude that ASICs have a credible, specific, and substantial utility. The information provided in the Application sufficiently connects the activity of ASICs with specific diseases states, including ischaemic pain and neurodegeneration. Additionally, I believe that numerous post-filing publications investigating the role of ASICs in ischaemic pain and neurodegeneration confirm that ASICs are involved in these disease states, as asserted in the Application. Thus, I believe that one skilled in the art would accept that the subject matter in the claims possesses the asserted utility in view of the Application alone or in combination with relevant post-filing publications.

6. The teachings of the Application do convey to one of ordinary skill in the art that the claimed subject matter is involved in ischaemic pain sensation. Pain caused by acid is believed to be mediated by proton-activated cationic channels in sensory neurons (See page 1, line 15). ASICs are proton-activated cationic channels and are located in sensory neurons (See page 16, line 10; page 17, line 24; and Figs. 5 and 8). Therefore, one skilled in the art would

consider that the localization and properties of ASICs to be probative that activation of the channels plays a role in the sensation acid-induced pain.

7. The teachings of the Application do convey to one of ordinary skill in the art that the claimed subject matter is involved neurodegeneration. ASICs are expressed in the brain (See page 18, line 2 and Fig. 7). ASICs are functionally equivalent and homologous to MDEG. Like ASICs, MDEG are amilioride-sensitive cationic channels. Active mutants of MDEG are responsible for cell death, thus the hyperactivity of cationic channels is implicated in neurodegeneration (See page 3, line 3). Therefore, one skilled in the art would consider that the localization and properties of ASICs and their similarities to MDEG to be probative of a role in neurodegeneration.

8. I consider that one of ordinary skill in the art would also accept that the claimed subject matter possesses a credible, specific, and substantial utility in view of the Application and post-filing publications. For example, Pignataro et al., Mazzuca et al., Wultsch et al., and Sluka et al. investigate ASICs with respect to pain and neurodegeneration, and confirm that the claimed channels are involved in the disease states of neurodegeneration and pain sensation, as asserted in the Application. Furthermore, I believe that the post-filing publications that investigate the role of ASICs in neurodegeneration and pain follow from the information disclosed in the Application, thus confirming that those skilled in the art accepted the asserted utilities at the time of filing.

9. I consider Pignataro et al., (2007) *Brain*, 130: 150-58 as providing evidence that demonstrates the role of ASICs in neurodegeneration, as asserted in the Application. The authors demonstrated that psalmotoxin, a tarantula-derived ASIC1a blocker, has a significant neuro-protective effect on murine models of ischaemic brain injury. Pignataro also demonstrates that ischaemic brain tissue is subject of dynamic changes in pH, which reaches values capable of activating ASIC1a at different phases of injury. The Pignataro study confirms the Applicants' assertions in their Specification that ASICs play a role in neurodegeneration caused by ischaemic and acidic brain injury.

10. Further, I consider Mazzuca et al., Wultsch et al., and Sluka et al. as providing evidence that demonstrates the role of ASICs in pain sensation, as asserted in the Application. The authors of Mazzuca show that ASIC1a is an important molecular target for treating both acute and neuropathic pain. The authors observed an anti-nocioceptive effect following the administration of ASIC1a antisense oligodeoxynucleotides and psalmotoxin, thus verifying a specific and significant role of ASIC1a in pain sensation.

11. Additionally, I understand recent murine knockout studies examining the role of ASIC3 in pain as confirming the assertion in the Application that ASICs play a role pain sensation. The authors of Wultsch et al. measured c-Fos, a marker of neuronal excitation, in the gastritis-induced acid hyperresponsiveness in ASIC2 and ASIC3 knockout mice. This data indicates that ASIC2-/- mice, unlike ASIC3-/- mice, developed gastric hyperresponssiveness. Therefore, the presented data suggests that ASIC3 is a target for therapeutic management of hyperalgesia. Another experiment by Sluka et al. tested response to mechanical and thermal pain stimuli on ASIC3-knockout mice and mice infected with an ASIC3-vector. Sluka demonstrates that ASIC3 is responsible for mechanical hyperalgesia and is critical to the development of hyperalgesia that results from muscle injury. I believe that one skilled in the art in view of these publications would not only appreciate the connection between ASICs and pain sensation, but that they would also believe that this study draws on the information and asserted utility in the Application.

12. Further, I do not consider the fact that the ASIC family is diverse is dispositive of the asserted utilities. The Application provides specific evidence and information that is probative of the asserted role of ASICs in pain and neurodegeneration. Therefore, even if there were evidence that an ASIC might possess an additional role in a different pathway or a different part of the body, it would not immediately contradict the assertion that ASICs are directly involved in pain and neurodegeneration.

13. The November 29, 2006 Official Action also states that the Application does not provide one of ordinary skill in the art with sufficient teaching to enable one skilled in the art to make and use the claimed subject matter because the Application does not provide a credible, specific, and substantial utility. As stated above, I believe that the Application sufficiently establishes utility of ASICs in the disease pathways of pain and neurodegeneration. Therefore, I believe that that one of ordinary skill in the art could make and use the claimed channels for purposes related to these disease states.

14. The undersigned declares that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

__21 Nov 2007____ _____
Date .....

CURRICULUM VITAE

Name: Peter Anthony McNaughton

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Date of Birth: 17.8.49

Place of Birth: Auckland, New Zealand

Nationality: Dual New Zealand and British (naturalized 1984)

Marital Status: Married, 4 children.

Education:

1962-1966	Auckland Grammar School, New Zealand.
1967-1970	Auckland University, studying for BSc (Hons) in Physics. Sir George Grey Prize for top science student in the University.
1971	Graduated BSc (Hons), Class I.
1971	Awarded Rhodes Scholarship for study in Oxford.
1971-1974	Balliol College, Oxford, studying for D.Phil. in Physiology. Graduated D.Phil. (equivalent of PhD)

Principal posts held:

1974-1978	Research Fellow, Clare College, Cambridge.
1978-1983	University Demonstrator, Physiological Laboratory, Cambridge.
1983-1991	University Lecturer, Physiological Laboratory, Cambridge.
1991 – 1999	Halliburton Professor of Physiology and Head of Dept. of Physiology, King's College London
1999 – present	Sheild Professor of Pharmacology and Head of Dept. of Pharmacology, University of Cambridge

EXHIBIT A

Part-time etc posts:	1977-1978	Elmore Medical Research Student, Physiological Laboratory, Cambridge.
	1983-1991	Fellow and Director of Studies in Physiology, Christ's College, Cambridge.
	1988-1989	Nuffield Science Research Fellow
	1989-1991	Director of Studies in Medicine, Christ's College, Cambridge
	1993-1996	Dean of Basic Medical Sciences, King's College London
	1999-present	Wolf Fellow in Pharmacology of Christ's College, Cambridge

Membership of Research Council Boards etc:

1996-2000	Member of Biochemistry and Cell Biology Panel, Biotechnology and Biological Sciences Research Council (BBSRC).
1998-2002	Chairman, Bio-imaging Initiative Panel, BBSRC
1998-2001	Member of Neuroscience Board, Wellcome Trust
2001-2004	Member of Neurone Initiative Panel, BBSRC
2001-present	Member of Advisory Board, Medical Research Council
2001	Member of BBSRC Institute Assessment Panel
2002	Member of selection panel for Ramon y Cajal Fellowships, Spanish Foundation for Science and Technology
2003-6	Member of Performance Based Research Fund Biological Sciences panel, New Zealand (equivalent of UK Research Assessment Exercise)
2007-present	Member of BBSRC Strategy Panel "The Healthy Organism"

Scientific societies:	1979 - present	Member, Physiological Society
	1988 - 92	Committee Member, Physiological Society
	1989 - 92	Manager of the Dale and Rushton Funds, Physiological Society
	1999 - present	Member, British Pharmacological Society

Honorary positions:	1998 - 2003	Honorary Professor, Dept. of Optometry and Vision Sciences, University of Wales Cardiff.

Grants in last 5 years (all are with P. McNaughton as sole applicant)

1998 – 2001	"Signalling pathways in noiceptive neurones" MRC, £223k
1998 – 2001	"Molecular and cellular basis of sensitivity regulation in nociceptive neurones" BBSRC, £216k.
1999 – 2002	"Molecular mechanism and modulation of expression of P-glycoprotein, a plasma membrane transporter" BBSRC, £270k
2000 – 4	"Regulation of expression of bradykinin receptors in nociceptive neurons" Wellcome Trust, £187k
2001 – 4	"Pharmacological and physiological properties of visceral nerves" Glaxo SmithKline, £77k.
2002 – 5	"Molecular processes controlling activation of the heat-sensitive ion channel, VR1" Merck, Sharpe & Dohme Ltd, £61k
2002 – 5	"Role of phosphorylation in the modulation of thermal sensation" BBSRC, £196k
2002 – 5	"Molecular mechanisms and functional roles of acid-sensing ion channels" BBSRC, £194k
2004 – 7	"Involvement of the hyperpolarisation-activated current Ih in nociceptor function" Organon Inc., £30k **Current**
2005 – 8	"Signalling pathways and scaffolding proteins modulating the activity of the heat and capsaicin receptor, TRPV1." BBSRC, £258k. **Current**
2005 – 8	"The cellular basis of magnetic sensation" BBSRC, £241k **Current**

2007 – 10	"Structure and function of candidate magnetite-based magnetoreceptor cells" Human Frontiers Science Program, $USD 1,320,000 **Current**
2008 – 11	"Modulation of thermo-TRP ion channel activity by phosphorylation and trafficking to the membrane" BBSRC, £404,500 **Current**

PUBLICATIONS

Full papers and refereed reviews:

McNaughton, P.A. and Matthews, R.E.F. (1971). Sedimentation of small viruses at very low concentrations. *Virology*, **45** : 1-9.

Brown, H.F., McNaughton, P.A., Noble, D. and Noble, S.J. (1975). Adrenergic control of cardiac pacemaker currents. *Phil. Trans. Roy. Soc. Lond. B.*, **270** : 527-537.

Hunter, P.J., McNaughton, P.A. and Noble, D. (1975). Analytical models of propagation in excitable cells. *Prog. Biophys. Mol. Biol.*, **30** : 99-144.

Baker, P.F. and McNaughton, P.A. (1976). Kinetics and energetics of calcium efflux from intact squid giant axons. *J. Physiol.*, **259** : 103-144.

Baker, P.F. and McNaughton, P.A. (1978). The influence of extracellular calcium binding on the calcium efflux from squid axons. *J. Physiol.*, **276** : 127-150.

Detwiler, P.B., Hodgkin, A.L. and McNaughton, P.A. (1978). A surprising property of electrical spread in the network of rods in the turtle's retina. *Nature*, **274** : 562-565.

Di Francesco, D. and McNaughton, P.A. (1979). The effects of calcium on outward membrane currents in the cardiac Purkinje fibres. *J. Physiol.*, **289** : 347-373.

Detwiler, P.B., Hodgkin, A.L. and McNaughton, P.A. (1980). Temporal and spatial characteristics of the voltage responses of rods in the retina of the snapping turtle. *J. Physiol.*, **300** : 213-250.

McNaughton, P.A., Yau, K.-W. and Lamb, T.D. (1980). Spread of activation and desensitization in rod outer segments. *Nature*, **283** : 85-87.

Lamb, T.D., McNaughton, P.A. and Yau, K.-W. (1981). Spatial spread of activation and background desensitization in toad rod outer segments. *J. Physiol.*, **319** : 463-496.

Yau, K.-W., McNaughton, P.A. and Hodgkin, A.L. (1981). Effect of ions on the light-sensitive current in retinal rods. *Nature*, **292** : 502-505.

Hodgkin, A.L., McNaughton, P.A., Nunn, B.J. and Yau, K.-W. (1984). Effect of ions on retinal rods from Bufo marinus. *J. Physiol.*, **350** : 649-680.

Hodgkin, A.L., McNaughton, P.A. and Nunn, B.J. (1985). The ionic selectivity and calcium dependence of light-sensitive channels in retinal rods from Bufo marinus. *J. Physiol.*, **358** : 447-468.

Cervetto, L. and McNaughton, P.A. (1986). The effects of phosphodiesterase inhibitors and lanthanum ions on the light-sensitive current of toad retinal rods. *J. Physiol.*, **370** : 91-109.

McNaughton, P.A., Cervetto, L. and Nunn, B.J. (1986). Measurement of the intracellular free calcium concentration in salamander rods. *Nature*, **322** : 261-263.

Hodgkin, A.L., McNaughton, P.A. and Nunn, B.J. (1987). Measurement of sodium-calcium exchange in salamander rods. *J. Physiol.*, **391** : 347-370.

Lagnado, L., Cervetto, L. and McNaughton, P.A. (1988). Ion transport by the Na:Ca exchange in isolated rod outer segments. *PNAS* **85** : 4548-4552.

Cervetto, L., Lagnado, L., Perry, R.J., Robinson, D.W. and McNaughton, P.A. (1989). Extrusion of calcium from rod outer segments is driven by both sodium and potassium gradients. *Nature* **337** : 740-743.

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Perry, R.J. & McNaughton, P.A. (1991). Response properties of cones from the retina of the tiger salamander. *Journal of Physiology* **433**, 561-587.

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Bonnington, J.K. & McNaughton, P.A. (2003). Signalling pathways involved in the sensitisation of mouse nociceptive neurones by nerve growth factor. *J. Physiol.* **551**, 433 – 446.

Vellani, V. & McNaughton, P.A. (2003) Involvement of protein kinase C in the sensation of pain. In: **Protein Kinase C (PKC)**, 2nd edition. Ed. Dekker, L.V. Landes Bioscience, Georgetown, Texas.

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McNaughton, P.A. (2004) Pain transduction: gating and modulation of ion channels. In: **Transduction channels in sensory cells.** Ed. Frings, S. & Bradley, J. Wiley-VCH, Germany.

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(N.B. This paper was featured in a Nature Research Highlights article in *Nature*, **438**, pg. 893, 2005)

Vellani, V., Colucci, M., Lattanzi, R., Giannini, E., Negri, L., Melchiorri, P. and McNaughton, P.A. (2006) Sensitization of TRPV1 by the prokineticin receptor agonist Bv8. *J. Neurosci.* **26**, 5109 – 16.

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Zhang, X. and McNaughton, P.A. (2006) Why pain gets worse: the mechanism of heat hyperalgesia. *Journal of General Physiology* **128**, 491-493.

Huang, J., Zhang, X. and McNaughton, P.A. (2006) Modulation of temperature-sensitive TRP channels. *Seminars in Cell and Developmental Biology* **17**, 638 – 45.

Smith, E. St J., Cadiou, H. & McNaughton, P.A. (2007) Arachidonic acid potentiates acid-sensing ion channels in rat sensory neurons by a direct action. *Neuroscience* **145**, 686-98.

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Review Articles:

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Yau, K.-W., Lamb, T.D. and McNaughton, P.A. (1981). Spread of excitation and background adaptation in the rod outer segment. In: **Current Topics in Membranes and Transport**, ed. W.H. Miller. Academic Press: New York.

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